COPAXONE - glatiramer acetate injection
TEVA Neuroscience, Inc.

DESCRIPTION

COPAXONE® is the brand name for glatiramer acetate (formerly known as copolymer-1). Glatiramer acetate, a member of the Glatiramoid family of compounds and the active ingredient of COPAXONE®, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000 – 9,000 daltons. Glatiramer acetate is identified by specific antibodies.
Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:

$$(Glu, Ala, Lys, Tyr)_x \bullet xCH_3COOH$$
$$(C_5H_9NO_4 \bullet C_3H_7NO_2 \bullet C_6H_{14}N_2O_2 \bullet C_9H_{11}NO_3)_x \bullet xC_2H_4O_2$$
CAS - 147245-92-9

COPAXONE® Injection is a clear, colorless to slightly yellow, sterile, non-pyrogenic solution for subcutaneous injection. Each 1.0 mL of solution contains 20 mg of glatiramer acetate and 40 mg of mannitol, USP. The pH range of the solution is approximately 5.5 to 7.0. The biological activity of COPAXONE® is determined by its ability to block the induction of EAE in mice.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism(s) by which glatiramer acetate exerts its effects in patients with Multiple Sclerosis (MS) is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in several animal species through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and *in vitro* systems suggest that upon its administration, glatiramer acetate-specific suppressor T-cells are induced and activated in the periphery.
Because glatiramer acetate can modify immune functions, concerns exist about its potential to alter naturally occurring immune responses. Results of a limited battery of tests designed to evaluate this risk produced no finding of concern; nevertheless, there is no logical way to absolutely exclude this possibility (see **PRECAUTIONS**).

Pharmacokinetics

Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support the assumption that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Nevertheless, larger fragments of glatiramer acetate can be recognized by glatiramer acetate-reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.

Clinical Trials

Evidence supporting the effectiveness of glatiramer acetate in decreasing the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RR MS) derives from two placebo-controlled trials, both of which used a glatiramer acetate dose of 20 mg/day. (No other dose or dosing regimen has been studied in placebo-controlled trials of RR MS.)
One trial was performed at a single center. It enrolled 50 patients who were randomized to receive daily doses of either glatiramer acetate, 20 mg subcutaneously, or placebo (glatiramer acetate, n=25; placebo, n=25). Patients were diagnosed with RR MS by standard criteria, and had had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Disability Scale Score (DSS), a standard scale ranging from 0–Normal to 10–Death due to MS. A score of 6 is defined as one at which a patient is still ambulatory with assistance; a score of 7 means the patient must use a wheelchair.
Patients were examined every 3 months for 2 years, as well as within several days of a presumed exacerbation. To confirm an exacerbation, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the neurological signs for at least 48 hours).
The protocol-specified primary outcome measure was the proportion of patients in each treatment group who remained exacerbation free for the 2 years of the trial, but two other important outcomes were also specified as endpoints: 1) the frequency of attacks during the trial, and 2) the change in the number of attacks compared with the number which occurred during the previous 2 years.
Table 1 presents the values of the three outcomes described above, as well as several protocol specified secondary measures. These values are based on the intent-to-treat population (i.e., all patients who received at least 1 dose of treatment and who had at least 1 on-treatment assessment):

Table 1: Study 1 Efficacy Results

Outcome	Glatiramer Acetate (N=25)	Placebo (N=25)	P-Value
% Relapse-Free Patients	14/25 (56%)	7/25 (28%)	0.085
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate Compared to Pre-Study	3.2	1.6	0.025
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

Progression was defined as an increase of at least 1 point on the DSS, persisting for at least 3 consecutive months.

The second trial was a multicenter trial of similar design which was performed in 11 US centers. A total of 251 patients (glatiramer acetate, 125; placebo, 126) were enrolled. The primary outcome measure was the Mean 2-Year Relapse Rate. The table below presents the values of this outcome for the intent-to-treat population, as well as several secondary measures:

Table 2: Study 2 Efficacy Results

Outcome	Glatiramer Acetate (N=125)	Placebo (N=126)	P-Value
Mean No. of Relapses	1.19/2 years	1.68 /2 years	0.055
% Relapse-Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Progression-Free Patients	98/125 (78%)	95/126 (75%)	0.48
Mean Change in DSS	-0.05	+0.21	0.023

In both studies glatiramer acetate exhibited a clear beneficial effect on relapse rate, and it is based on this evidence that glatiramer acetate is considered effective.

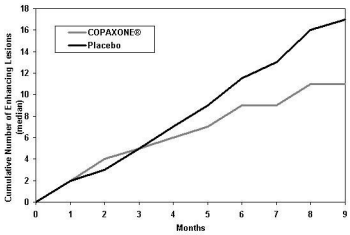
A third study was a multi-national study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RR MS (119 on glatiramer acetate and 120 on placebo) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over the nine months. Table 3 summarizes the results for the primary outcome measure monitored during the trial for the intent-to-treat cohort.

Table 3: Study 3 MRI Results

Outcome	Glatiramer Acetate (N=119)	Placebo (N=120)	P-Value
Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	11	17	0.0030

The following figure displays the results of the primary outcome on a monthly basis.

Figure 1: Median Cumulative Number of Gd-Enhancing Lesions



p= 0.0030 for the difference between the placebo-treated (n=120) and glatiramer acetate-treated (n=119) groups

INDICATIONS AND USAGE

COPAXONE® Injection is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis.

CONTRAINDICATIONS

COPAXONE® Injection is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

WARNINGS

The only recommended route of administration of COPAXONE® Injection is the subcutaneous route. COPAXONE® Injection should not be administered by the intravenous route.

PRECAUTIONS

General

Patients should be instructed in self-injection techniques to assure the safe administration of COPAXONE® Injection (see **PRECAUTIONS: Information for Patients** and the **COPAXONE® INJECTION PATIENT INFORMATION** Leaflet). Current data indicate that no special caution is required for patients operating an automobile or using complex machinery.

Considerations Regarding the Use of a Product Capable of Modifying Immune Responses

Because glatiramer acetate can modify immune response, it could possibly interfere with useful immune functions. For example, treatment with glatiramer acetate might, in theory, interfere with the recognition of foreign antigens in a way that would undermine the body's tumor surveillance and its defenses against infection. There is no evidence that glatiramer acetate does this, but there has as yet been no systematic evaluation of this risk. Because glatiramer acetate is an antigenic material, it is possible that its use may lead to the induction of host responses that are untoward, but systematic surveillance for these effects has not been undertaken.

Although glatiramer acetate is intended to minimize the autoimmune response to myelin, there is the possibility that continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled trial of 125 RR MS patients given glatiramer acetate, 20 mg, subcutaneously every day for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the lgG subtype-and predominantly of the lgG-1 subtype. No lgE type antibodies could be detected in any of the 94 sera tested; nevertheless, anaphylaxis can be associated with the administration of most any foreign substance, and therefore, this risk cannot be excluded.

Information for Patients

To assure safe and effective use of COPAXONE® Injection, the following information and instructions should be given to patients:

1. Inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while taking this medication.
2. Inform your physician if you are nursing.
3. Do not change the dose or dosing schedule without consulting your physician.
4. Do not stop taking the drug without consulting your physician.

Patients should be instructed in the use of aseptic techniques when administering COPAXONE® Injection. Appropriate instructions for the self-injection of COPAXONE® Injection should be given, including a careful review of the **COPAXONE® INJECTION PATIENT INFORMATION** Leaflet. The first injection should be performed under the supervision of an appropriately qualified

health care professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically reevaluated. Patients should be cautioned against the reuse of needles or syringes and instructed in safe disposal procedures. They should use a puncture-resistant container for disposal of used needles and syringes. Patients should be instructed on the safe disposal of full containers according to local laws.

Awareness of Adverse Reactions: Physicians are advised to counsel patients about adverse reactions associated with the use of COPAXONE® Injection (see **ADVERSE REACTIONS** section). In addition, patients should be advised to read the **COPAXONE®INJECTION PATIENT INFORMATION** Leaflet and resolve any questions regarding it prior to beginning COPAXONE® Injection therapy.

Laboratory Tests

Data collected during premarketing development do not suggest the need for routine laboratory monitoring.

Drug Interactions

Interactions between COPAXONE® Injection and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® Injection with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. COPAXONE® Injection has not been formally evaluated in combination with Interferon beta.

Drug/Laboratory Test Interactions

None are known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a two-year carcinogenicity study, mice were administered up to 60 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m^2 basis). No increase in systemic neoplasms was observed. In males of the high dose group (60 mg/kg/day), but not in females, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.

In a two-year carcinogenicity study, rats were administered up to 30 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m^2 basis). No increase in systemic neoplasms was observed.

Mutagenesis

Glatiramer acetate was not mutagenic in four strains of *Salmonella typhimurium* and two strains of *Escherichia coli* (Ames test) or in the *in vitro* mouse lymphoma assay in L5178Y cells. Glatiramer acetate was clastogenic in two separate *in vitro* chromosomal aberration assays in cultured human lymphocytes; it was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

In a multigeneration reproduction and fertility study in rats, glatiramer acetate at subcutaneous doses of up to 36 mg/kg (18 times the human therapeutic dose on a mg/m^2 basis) had no adverse effects on reproductive parameters.

Pregnancy

Pregnancy Category B. No adverse effects on embryofetal development occurred in reproduction studies in rats and rabbits receiving subcutaneous doses of up to 37.5 mg/kg of glatiramer acetate during the period of organogenesis (18 and 36 times the therapeutic human dose on a mg/m^2 basis, respectively). In a prenatal and postnatal study in which rats received subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, glatiramer acetate should be used during pregnancy only if clearly needed.

Labor and Delivery

In a prenatal and postnatal study, in which rats received subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery were observed. The relevance of these findings to humans is unknown.

Nursing Mothers

It is not known whether glatiramer acetate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COPAXONE® is administered to a nursing woman.

Pediatric Use

The safety and efficacy of COPAXONE® Injection have not been established in individuals under 18 years of age.

Use in the Elderly

COPAXONE® Injection has not been studied specifically in elderly patients.

Use in Patients with Impaired Renal Function

The pharmacokinetics of glatiramer acetate in patients with impaired renal function have not been determined.

ADVERSE REACTIONS

During premarketing clinical trials approximately 900 individuals received at least one dose of glatiramer acetate.
In controlled clinical trials the most commonly observed adverse experiences associated with the use of glatiramer acetate and not seen at an equivalent frequency among placebo-treated patients were: injection site reactions, vasodilatation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety, and hypertonia.
Approximately 8% of the 893 subjects receiving glatiramer acetate discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: injection site reaction (6.5%), vasodilatation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness, and tremor.

Immediate Post-Injection Reaction

Approximately 10% of MS patients exposed to glatiramer acetate in premarketing studies experienced a constellation of symptoms immediately after injection that included flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. In clinical trials, the symptoms were generally transient and self-limited and did not require specific treatment. In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. During the postmarketing period, there have been reports of patients with similar symptoms who received emergency medical care.
Whether an immunologic or non-immunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

Chest Pain

Approximately 21% of glatiramer acetate patients in the pre-marketing controlled studies (compared to 11% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of this chest pain to an injection of glatiramer acetate was not always known. The pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. There has been only one episode of chest pain during which a full EKG was performed; that EKG showed no evidence of ischemia. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown.
Incidence in Controlled Clinical Studies: The following table lists treatment-emergent signs and symptoms that occurred in at least 2% of MS patients treated with glatiramer acetate in the pre-marketing placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with glatiramer acetate than in patients treated with placebo. These trials include the first two controlled trials in RR MS patients and a controlled trial in patients with Chronic-Progressive MS. Adverse reactions were usually mild in intensity.
The prescriber should be aware that these figures cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis on which to estimate the relative contribution of drug and nondrug factors to the adverse reaction incidences in the population studied.
Controlled Trials in Patients with Multiple Sclerosis: Incidence of Glatiramer Acetate Adverse Reactions ≥2% and More Frequent than Placebo

	Glatiramer Acetate (N = 201)		Placebo (N = 206)	
Preferred Term	**N**	**%**	**N**	**%**
Body as a Whole				
Asthenia	83	41	78	38
Back Pain	33	16	30	15

Bacterial Infection	11	5	9	4
Chest Pain	43	21	22	11
Chills	8	4	2	1
Cyst	5	2	1	0
Face Edema	12	6	2	1
Fever	17	8	15	7
Flu Syndrome	38	19	35	17
Infection	101	50	99	48
Injection Site Erythema	132	66	40	19
Injection Site Hemorrhage	11	5	6	3
Injection Site Induration	26	13	1	0
Injection Site Inflammation	98	49	22	11
Injection Site Mass	54	27	21	10
Injection Site Pain	147	73	78	38
Injection Site Pruritus	80	40	12	6
Injection Site Urticaria	10	5	0	0
Injection Site Welt	22	11	5	2
Neck Pain	16	8	9	4
Pain	56	28	52	25
Cardiovascular System				
Migraine	10	5	5	2
Palpitations	35	17	16	8
Syncope	10	5	5	2
Tachycardia	11	5	8	4
Vasodilatation	55	27	21	10

Digestive System					
	Anorexia	17	8	15	7
	Diarrhea	25	12	23	11
	Gastroenteritis	6	3	2	1
	Gastrointestinal Disorder	10	5	8	4
	Nausea	44	22	34	17
	Vomiting	13	6	8	4
Hemic and Lymphatic System					
	Ecchymosis	16	8	13	6
	Lymphadenopathy	25	12	12	6
Metabolic and Nutritional					
	Edema	5	3	1	0
	Peripheral Edema	14	7	8	4
	Weight Gain	7	3	0	0
Musculoskeletal System					
	Arthralgia	49	24	39	19
Nervous System					
	Agitation	8	4	4	2
	Anxiety	46	23	40	19
	Confusion	5	2	1	0
	Foot Drop	6	3	4	2
	Hypertonia	44	22	37	18
	Nervousness	4	2	2	1
	Nystagmus	5	2	2	1
	Speech Disorder	5	2	3	1
	Tremor	14	7	7	3
	Vertigo	12	6	11	5

Respiratory System				
Bronchitis	18	9	12	6
Dyspnea	38	19	15	7
Laryngismus	10	5	7	3
Rhinitis	29	14	27	13
Skin and Appendages				
Erythema	8	4	4	2
Herpes Simplex	8	4	6	3
Pruritus	36	18	26	13
Rash	37	18	30	15
Skin Nodule	4	2	1	0
Sweating	31	15	21	10
Urticaria	9	4	5	2
Special Senses				
Ear Pain	15	7	12	6
Eye Disorder	8	4	1	0
Urogenital System				
Dysmenorrhea	12	6	10	5
Urinary Urgency	20	10	17	8
Vaginal Moniliasis	16	8	9	4

Other events which occurred in at least 2% of glatiramer acetate patients but were present at equal or greater rates in the placebo group included:
Body as a Whole: Headache, injection site ecchymosis, accidental injury, abdominal pain, allergic rhinitis, neck rigidity, and malaise.
Digestive System: Dyspepsia, constipation, dysphagia, fecal incontinence, flatulence, nausea and vomiting, gastritis, gingivitis, periodontal abscess, and dry mouth.
Musculoskeletal: Myasthenia and myalgia.
Nervous System: Dizziness, hypesthesia, paresthesia, insomnia, depression, dysesthesia, incoordination, somnolence, abnormal gait, amnesia, emotional lability, Lhermitte's sign, abnormal thinking, twitching, euphoria, and sleep disorder.
Respiratory System: Pharyngitis, sinusitis, increased cough, and laryngitis.
Skin and Appendages: Acne, alopecia, and nail disorder.
Special Senses: Abnormal vision, diplopia, amblyopia, eye pain, conjunctivitis, tinnitus, taste perversion, and deafness.
Urogenital System: Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.
Data on adverse reactions occurring in the controlled clinical trials were analyzed to evaluate differences based on sex. No clinically significant differences were identified. Ninety-two percent of patients in these clinical trials were Caucasian. This percentage reflects

the racial composition of the MS population. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically relevant age subgroups.

Laboratory analyses were performed on all patients participating in the clinical program for glatiramer acetate. Clinically significant laboratory values for hematology, chemistry, and urinalysis were similar for both glatiramer acetate and placebo groups in blinded clinical trials. No patient receiving glatiramer acetate withdrew from any trial because of abnormal laboratory findings.

Other Adverse Events Observed During Clinical Trials

Glatiramer acetate was administered to 979 individuals during premarketing clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators, using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into standardized categories using COSTART dictionary terminology. All reported events occurring at least twice and potentially important events occurring once are listed below, except those already listed in the previous table, those too general to be informative, trivial events, and other reactions which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group. Additional adverse reactions reported during the post-marketing period are included.

Events are further classified within body system categories and listed in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *Rare* adverse events are those occurring in less than 1/1000 patients.

Body as a Whole:

Frequent: Injection site edema, injection site atrophy, abscess, injection site hypersensitivity.

Infrequent: Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma, and photosensitivity reaction.

Cardiovascular:

Frequent: Hypertension.

Infrequent: Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension, and varicose veins.

Digestive:

Infrequent: Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration, and duodenal ulcer.

Endocrine:

Infrequent: Goiter, hyperthyroidism, and hypothyroidism.

Gastrointestinal:

Frequent: Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis.

Hemic and Lymphatic:

Infrequent: Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly.

Metabolic and Nutritional:

Infrequent: Weight loss, alcohol intolerance, Cushing’s syndrome, gout, abnormal healing, and xanthoma.

Musculoskeletal:

Infrequent: Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis.

Nervous:

Frequent: Abnormal dreams, emotional lability, and stupor.

Infrequent: Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression, and transient stupor.

Respiratory:

Frequent: Hyperventilation, hay-fever.

Infrequent: Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

Skin and Appendages:

Frequent: Eczema, herpes zoster, pustular rash, skin atrophy, and warts.

Infrequent: Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash.

Special Senses:

Frequent: Visual field defect.

Infrequent: Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

Urogenital:

Frequent: Amenorrhea, hematuria, impotence, menorrhagia, suspicious papanicolaou smear, urinary frequency and vaginal hemorrhage.

Infrequent: Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, carcinoma *in situ* cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Postmarketing Clinical Experience

Postmarketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE® (glatiramer acetate for injection) not mentioned above that have been received since market introduction and that may have or not have causal relationship to the drug include the following:

Body as a Whole: sepsis; LE syndrome; hydrocephalus; enlarged abdomen; injection site hypersensitivity; allergic reaction; anaphylactoid reaction, injection site skin necrosis

Cardiovascular System: thrombosis; peripheral vascular disease; pericardial effusion; myocardial infarct; deep thrombophlebitis; coronary occlusion; congestive heart failure; cardiomyopathy; cardiomegaly; arrhythmia; angina pectoris

Digestive System: tongue edema; stomach ulcer; hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

Hemic and Lymphatic System: thrombocytopenia; lymphoma-like reaction; acute leukemia

Metabolic and Nutritional Disorders: hypercholesterolemia

Musculoskeletal System: rheumatoid arthritis; generalized spasm

Nervous System: myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain edema; abnormal dreams; aphasia; convulsion; neuralgia

Respiratory System: pulmonary embolus; pleural effusion; carcinoma of lung; hay fever

Special Senses: glaucoma; blindness; visual field defect

Urogenital System: urogenital neoplasm; urine abnormality; ovarian carcinoma; nephrosis; kidney failure; breast carcinoma; bladder carcinoma; urinary frequency

Lipoatrophy Associated with Subcutaneous Use

At injection sites, localized lipoatrophy has have been reported during the postmarketing experience. Lipoatrophy may occur at various times after treatment onset (sometimes after several months) and is thought to be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events the patient should be advised to follow proper injection technique and to rotate injection areas and sites on a daily basis. COPAXONE® should not be injected in sites where lipoatrophy has occurred. (See **PATIENT INFORMATION**)

DRUG ABUSE AND DEPENDENCE

No evidence or experience suggests that abuse or dependence occurs with COPAXONE® Injection therapy; however, the risk of dependence has not been systematically evaluated.

DOSAGE AND ADMINISTRATION

The recommended dose of COPAXONE® Injection for the treatment of RR MS is 20 mg/day injected subcutaneously.

Instructions for Use

Remove one blister with the syringe inside from the COPAXONE® Injection Pre-filled syringes package from the refrigerator. For refrigerated product, let the pre-filled syringe package stand at room temperature for 20 minutes to allow the solution to warm up to room temperature. Inspect the product visually and discard or return the product to the pharmacist before use if it contains any particulate matter.

Sites for self-injection include arms, abdomen, hips, and thighs. The pre-filled syringe is suitable for single use only; unused portions should be discarded. (See the **COPAXONE® Injection PATIENT INFORMATION** Leaflet for **INSTRUCTIONS FOR INJECTING COPAXONE®**.)

HOW SUPPLIED

COPAXONE® Injection is supplied as a single-use pre-filled syringe containing 1.0 mL of a clear, colorless to slightly yellow, sterile, non-pyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol, USP in cartons of 30 single-use pre-filled syringes, 33 alcohol preps (wipes) and instructions for use.

The recommended storage condition for the COPAXONE® Injection is refrigeration (2°C to 8°C / 36°F to 46°F). However, excursions from recommended storage conditions to room temperature conditions (15° to 30°C/ 59° to 86° F) for up to one month have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided.

COPAXONE® Injection contains no preservative. Do not use if the solution contains any particulate matter.

COPAXONE® Injection is available in packs of 30 single-use Pre-Filled Syringes (NDC 0088-1153-30).
Rx only.

PATIENT INFORMATION

COPAXONE® (glatiramer acetate injection)

Read this information carefully before you use COPAXONE®. Read the information you get when you refill your COPAXONE® prescriptions because there may be new information. This information does not take the place of your doctor's advice. Ask your doctor or pharmacist if you do not understand some of this information or if you want to know more about this medicine.

What is COPAXONE®?

COPAXONE® (co-PAX-own) is a medicine you inject to treat Relapsing-Remitting Multiple Sclerosis. Although COPAXONE® is not a cure, patients treated with COPAXONE® have fewer relapses.

Who should not use COPAXONE®?

- COPAXONE® is not recommended for use in pregnancy. So, tell your doctor if you are pregnant or if you plan to become pregnant while taking this medicine.
- Tell your doctor if you are nursing. It is not known if COPAXONE® is passed through the breast milk to the baby.
- Do not use COPAXONE® if you are allergic to glatiramer acetate or mannitol.

What are the possible side effects of COPAXONE®?

- **Call your doctor right away if you develop any of the following symptoms: hives, skin rash with irritation, dizziness, sweating, chest pain, trouble breathing, or severe pain at the injection site.** Do not give yourself any more injections until your doctor tells you to begin again.
- The most common side effects of COPAXONE® are redness, pain, swelling, itching, or a lump at the injection site. These reactions are usually mild and seldom require medical care.
- Some patients report a short-term reaction right after injecting COPAXONE®. This reaction can involve flushing (feeling of warmth and/or redness), chest tightness or pain with heart palpitations, anxiety, and trouble breathing. These symptoms generally appear within minutes after an injection, last a few minutes, then go away by themselves without further problems.
- A permanent depression under the skin at the injection site may occur, due to a local destruction of fat tissue.
- **If symptoms become severe, call the emergency phone number in your area.** Do not give yourself any more injections until your doctor tells you to begin again.

These are not all the possible side effects of COPAXONE®. For a complete list, ask your doctor or pharmacist. Tell your doctor about any side effects you have while taking COPAXONE®.

How should I use COPAXONE®?

- The recommended dose of COPAXONE® for the treatment of Relapsing-Remitting Multiple Sclerosis is 20 mg once a day injected subcutaneously (in the fatty layer under the skin).
- Look at the medicine in the pre-filled syringe. If the medicine is cloudy or has particles in it, do not use it. Instead, call Shared Solutions at 1-800-887-8100 for assistance.

- Have a friend or relative with you if you need help, especially when you first start giving yourself injections.
- Each pre-filled syringe should be used for only one injection. Do not reuse the pre-filled syringe. After use, throw it away properly.
- Do not change the dose or dosing schedule or stop taking the medicine without talking with your doctor.

How do I inject COPAXONE®?

There are 3 basic steps for injecting COPAXONE® pre-filled syringes:

1. Gather the materials.
2. Choose the injection site.
3. Give yourself the injection.

Step 1: Gather the materials

1. First, place each of the items you will need on a clean, flat surface in a well-lit area:

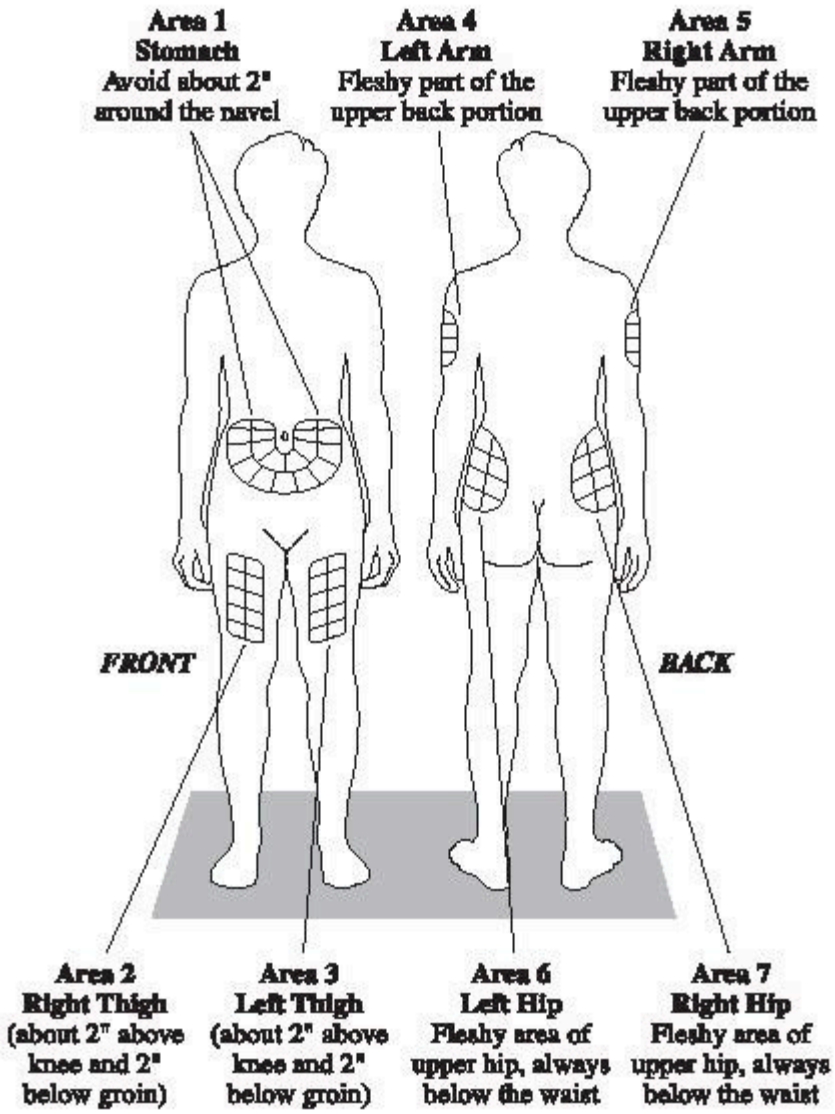
- 1 blister pack with COPAXONE® Pre-Filled Syringe

  Remove only 1 blister pack from the COPAXONE® Pre-Filled Syringe carton. Keep all unused syringes in the Pre-Filled Syringe carton and store them in the refrigerator.
- Alcohol prep (wipe)
- Dry cotton ball (not supplied)

2. Let the blister pack with the syringe inside warm up to room temperature for 20 minutes.
3. To prevent infection, wash and dry your hands. Do not touch your hair or skin after washing.
4. There may be small air bubbles in the syringe. To avoid loss of medicine when using COPAXONE® pre-filled syringes, do not expel (or do not attempt to expel) the air bubble from the syringe before injecting the medicine.

Step 2: Choose the injection site

- There are 7 possible injection areas on your body: arms, thighs, hips and lower stomach area (abdomen) (See Figure 1).



- Each day, pick a different injection area from one of the 7 areas. **Do not inject in the same area more than once a week**.
- Within each injection area there are multiple injection sites. Have a plan for rotating your injection sites. Keep a record of your injection sites, so you know where you have injected.
- There are some sites in your body that may be hard to reach for self-injection (like the back of your arm), and you may need help.
- Do not inject in sites where skin depression has occurred, because further injections in these sites may make the depression deeper.

Step 3: Give yourself the injection

1. Remove the syringe from its protective blister pack by peeling back the paper label. Before use, look at the liquid in the syringe. If it is cloudy or contains any particles, do not use it and call Shared Solutions at 1-800-887-8100 for assistance. If the liquid is clear, place the syringe on the clean, flat surface.
2. Choose an injection site on your body. Clean the injection site with a new alcohol prep and let the site air dry to reduce stinging.
3. Pick up the syringe as you would a pencil. Remove the needle shield from the needle.
4. With your other hand, pinch about a 2-inch fold of skin between your thumb and index finger (See Figure 2).
5. Insert the needle at a 90-degree angle (straight in), resting the heel of your hand against your body. When the needle is all the way in release the fold of skin (See Figure 3).

Figure 2

Figure 3

6. To inject the medicine, hold the syringe steady and push down the plunger.

7. When you have injected all of the medicine, pull the needle straight out.

8. Press a dry cotton ball on the injection site for a few seconds. **Do not rub the injection site.**

9. Throw away the syringe in a safe hard-walled plastic container.

What is the proper use and disposal of Pre-Filled Syringes?

Each Pre-Filled Syringe should be used for only 1 injection. Throw away all used Pre-Filled Syringes in a hard-walled plastic container, such as an empty liquid laundry detergent bottle. Keep the container closed tightly and out of the reach of children. When the container is full, check with your doctor, pharmacist, or nurse about proper disposal, as laws vary from state to state.

How should I store COPAXONE® Pre-Filled Syringes?

Keep the COPAXONE® Pre-Filled Syringe carton in the refrigerator, out of the reach of children.

The COPAXONE® package should be refrigerated as soon as you get it, at 36-46°F (2-8°C). If you cannot store COPAXONE® in a refrigerator, you can store it at room temperature, 59-86°F(15-30°C), for up to one month. Do not store COPAXONE® at room temperature for longer than one month. **Do not freeze COPAXONE®**. If a COPAXONE® pre-filled syringe freezes, throw it away in a proper container.

COPAXONE® is light sensitive. Protect it from light when not injecting. Do not use the pre-filled syringe if the solution contains particles or is cloudy.

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use COPAXONE® for a condition for which it was not prescribed. Do not give COPAXONE® to other people, even if they have the same condition you have. It may harm them.

This leaflet summarizes the most important information about COPAXONE®. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about COPAXONE® that is written for health professionals.

Also, you can call Shared Solutions for any questions about COPAXONE® and its use. The phone number for Shared Solutions is 1-800-887-8100.

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